In re Application of: Itskovitz-Eldor et al
Serial No.: 10/536,734
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Examiner: KIM, Taeyoon
Group Art Unit: 1651
Attorney Docket: 29601

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 193-202, 205, 214-234 are in this Application. Claims 194, 201 and 216-234 have been withdrawn from consideration. Claims 193, 195-200 and 202, 205, 214 and 215 have been rejected. Claims 195-198 have been amended herewith.

Claim Objections

The Examiner objects to claims 195-198 for informalities that relate to designation of claim steps. Claims 195-198 has now been amended rendering moot any objection with respect to this claim.

35 U.S.C. § 112 Rejections

The Examiner has rejected claim 198 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that claim 198 discloses a limitation to the culturing conditions and it is vague whether the culturing conditions include suspended cell cultures.

Claim 198 has now been amended to more clearly define the culturing conditions of the insulin producing cells which are indeed cultured as suspended cell clusters.

35 U.S.C. § 103 Rejections

The Examiner has rejected claims 193, 195-200 and 202, 205, 214 and 215 under U.S.C. 103(a) as being unpatentable over Lumelsky et al. in view of Dang et al. in further view of Ling et al.

The Examiner has further rejected claims 193, 214 and 215 under U.S.C. 103(a) as being unpatentable over Lumelsky et al. in view of Dang et al. in further view of Thomson et al.

As was argued in the previous response, the present methodology differs from that of Lumelsky in that it includes a method step which substantially increases the homogeneity of the resultant culture prior to expansion.

Following isolation of the progenitors from EBs, the present method employs an addition cell selection step which leads to formation of surface bound clusters. Such a step serves two purposes, it concentrates the endocrine progenitors into readily harvestable surface-bound clusters and it ensures that the clusters are substantially free of non-endocrine cells, since such cells cannot adhere to the substrate.

The Examiner states that although Lumelsky et al. do not teach this step, Dang et al. teach dissociation for the purpose of performing flow cytometry.

Claim 193 of the instant application actually states:

"subjecting said cells displaying at least one characteristic associated with a pancreatic islet cell progenitor phenotype to a second set of culturing conditions selected suitable for formation of surface bound cell clusters" and for "inhibiting growth of non insulin producing cells"

Dang et al. do not teach or suggest culturing the cells under such conditions, since as stated by the Examiner, Dang et al. dissociate the cells for the purpose of cell selection via flow cytometry and not for further culturing. The cells produced by Dang et al. are not subjected to culturing conditions which form clusters while inhibiting the growth of non insulin producing cells. In fact, Dang et al. do not describe or suggest further culturing, nor do they provide conditions which can be used for further culturing of clusters.

The Examiner further states that although Lumelsky et al. do not teach culturing conditions suitable for formation of clusters while inhibiting growth of non

insulin producing cells, since Lumelsky et al. utilize serum free media such as ITSF for the culture of pancreatic precursor cells and since these cells are plated onto a surface that permits adhesion of pancreatic endocrine stem or progenitor cells, the method of Lumelsky et al. inherently promotes formation of surface bound cell clusters which inhibiting growth of non insulin promoting cells.

Careful review of the teachings of Lumelsky et al. indicates that this is simply not the case, and that the method of Lumelsky et al. does not inherently produce the clusters of the present invention.

Section 0017 of US 2004/0121460 clearly sets forth the conditions used by Lumelsky et al.:

"Briefly, the ES cells were taken through 5 steps or stages. In stage 1 undifferentiated ES cells were cultured for 5 days in the presence of 15% fetal calf serum (FCS) on gelatin coated tissue culture dishes in the presence of LIF (1,400 U/ml). In stage 2 embryoid bodies (Ebs) were generated in the presence of FCS for 4 days in the presence or absence of LIF (1,000 U/ml.). In stage 3, the EBs were plated into ITSFn medium (Okabe et al., Mech. Dev. 59: 89-102, 1996) where over 10 days Nestin+ cells migrated from the cell aggregates. In stage 4 these Nestin+ cells were resuspended and expanded for 4 days in N2 medium containing bFGF, sonic hedgehog (Shh) and fibroblast growth factor-8 (FGF8). In stage 5 the medium was changed into N2 medium without bFGF, Shh or FGF8. These cells differentiated efficiently into neurons and astrocytes over a two week period." (emphasis added)

Thus, Lumelsky et al. directly plated the EBs and cultured them under conditions which permitted migration of Nestin-positive cells from the aggregates, no dissociation of EBs into cells is taught or suggested in US 2004/0121460, nor is further culturing taught.

Stage 3 of the method of Lumelsky et al. requires culturing of the EBs in ITSFn (which induces a Nestin+ phenotype) over a culturing period of days (10 days in this

case). Thus, culturing stage 3 of Lumelsky et al. is selected specifically for production of Nestin positive cells in the cultured EBs and facilitates subsequent migration of such cells out of the EBs. Modification of the method of Lumelsky et al. to include a step of cell dissociation is simply not suggested by any teaching of Lumelsky et al. or any other prior art reference cited by the Examiner.

Not withstanding the above, if one was motivated to 'modify' the method of Lumelsky et al. for the purpose of improving it, such an improvement would in all likelihood relate to steps involving differentiation of progenitors and not the one step that appears to be the core of the method of Lumelsky et al., namely culturing EBs under conditions suitable for formation and migration of Nestin-positive cells.

In view of the above amendments and remarks it is respectfully submitted that claims 193, 195-200, 202-205 and 214-215 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Enclosure:

- Petition for Extension (One Month)